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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/868,243	CARLIN ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 08/18/04 in response to the non-final Office Action mailed 05/18/04.

Status of Claims

2) Claims 1-39 have been canceled via the amendment filed 08/18/04.

New claims 40-49 have been added via the amendment filed 08/19/04.

Claims 40-49 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

5) The rejection of claims 1 and 5-12 made in paragraph 8 of the Office Action mailed 05/18/04 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is moot in light of Applicants' cancellation of the claims.

6) The rejection of claim 1 made in paragraph 9(a) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claims 5-7 made in paragraph 9(b) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

8) The rejection of claims 6 and 7 made in paragraph 9(c) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

9) The rejection of claim 6 made in paragraph 9(d) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

10) The rejection of claims 6 and 7 made in paragraph 9(e) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 5-12 made in paragraph 9(f) of the Office Action mailed 05/18/04 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 1 and 5-12 made in paragraph 11 of the Office Action mailed 05/18/04 under 35 U.S.C § 102(b) as being anticipated by Savarino *et al.* (*J. Infect. Dis.* 177: 796-799, March 1998 – Applicants' IDS) as evidenced by Holmgren *et al.* (WO 92/14487), is moot in light of Applicants' cancellation of the claims.

Response to Applicants' Arguments on Savarino *et al.*

13) With regard to the teachings of Savarino *et al.*, Applicants cite MPEP § 2131 and case law, and ask the question: 'Where in the reference is all of the limitations now set forth in the claims now present in the application?' Applicants contend that for the success of the vaccine composition of the invention, it is necessary to have at least three types of colonization factor antigens, each present in an amount of at least 100 micrograms. Applicants submit that the Savarino reference only states the types of colonization factor antigens and the number of killed *E. coli*, and that there is no control of the amount of the different colonization factor antigens present. Applicants point to the statement at lines 8 and 9 on page 2 of the present application and state that for product safety and efficiency, a vaccine composition must be non-infectious and contain defined amounts of active ingredients which are the same from batch to batch. Applicants assert that it is necessary for a vaccine composition to have a defined amount or at least a defined lower amount of antigens that trigger the immune response of the vaccinated patient. Applicants point to the first two lines on page 2 of the instant specification and state that there were problems in the cultivation of *E. coli* to obtain commercial quantities of the ETEC bacteria with

CFAs and their CS-antigen subcomponents, or with the scaling up of the production of ETEC bacteria having CFAs. Applicants cite parts of WO 95/33825 (US 5,935,838) and state that the publication disclosed how to obtain commercial quantities of the ETEC bacteria with CFAs and their SC antigen subcomponents, and to formalin-kill the bacteria for use as an oral vaccine against the ETEC bacteria. Applicants then cite of WO 95/33825's surprising finding in the scaling up of the production of ETEC that the bacteria lost their ability to produce CFAs more and more for each new generation, and that the loss of the ability of the bacteria to produce CFAs at temperatures above room temperature was accompanied by a loss of the regulatory gene localized in a plasmid in the bacteria. Applicants state that Savarino's ETEC/rCTB vaccine, E003, was produced by SBL Vaccin (Stockholm), and submit to the Office an 'Analysis Certificate, Reanalysis of the Lot no: E 003A'. The Analysis certificate is stated to depict the fimbrial antigen content in the ELISA test (Mab) showing that 'there were >20 μg/dose of each of CFA/I, CS1, CS2, CS4 and CS5'. With this, Applicants opine or conclude that SBL had trouble to produce higher amounts of the fimbrial antigen on *E. coli* at that time, and therefore cut-off was set at 20 μg. Applicants submit that the vaccine of the instant invention should contain at least 100 μg of each colonization factor antigen present in the vaccine composition.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth below under art rejection, Savarino *et al.* taught the vaccine claimed in the instant claims, i.e., an oral ETEC/rCTB vaccine produced by SBL Vaccin, Stockholm, comprising formalin-inactivated ETEC SBL101 expressing CFA/I; SBL104 expressing CS4+CS6; SBL105 expressing CS5+CS6; SBL106 expressing CS1; and SBL 107 expressing CS2+CS3 mixed with 1.0 mg of rCTB, wherein ST is removed. Savarino's vaccine is indeed non-infectious, and it proved safe and efficacious in adult humans. Nothing in Savario's disclosure indicates that the vaccine did not contain defined amounts of active ingredients. The fact that Savarino's ETEC vaccine was of acceptable safety and favorable immunogenicity (see last paragraph of 'Discussion') is indicative of the presence of defined amounts of the CFAs in the vaccine.

With regard to Applicants' conclusion of what is depicted in the submitted 'Analysis

Certificate, Reanalysis of the Lot no: E 003A', it should be noted that '>20 μg/dose of each of CFA/I, CS1, CS2, CS4 and CS5' does not necessarily mean that SBL had trouble to produce higher amounts of the fimbrial antigen on *E. coli* at that time, and therefore SBL set the cut-off to be at 20 μg. The phrase '>20 μg/dose of each of CFA/I, CS1, CS2, CS4 and CS5' in fact encompasses at least 100 μg. See the art rejection below for a detailed explanation of how Savarino's vaccine dose meets Applicants' claim limitation of 'at least 100 μg'. *Arguendo*, even if one viewed Savarino's teachings as not being anticipatory, the teachings of Savarino *et al.* render the instant claims obvious as explained below under the art rejection. Applicants' acknowledgment that WO 95/33825 (US 5,935,838) disclosed how to obtain commercial quantities of the ETEC bacteria with CFAs and the SC antigen subcomponents, and the prior art teachings made of record below document that it would have been well within the realm of routine experimentation to increase the CFA and CS antigen expression on Savarino's *E. coli* using art-known methods to produce the instant invention, as described below under the art rejection.

Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)*. 'When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.' *In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)*. Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best, 562 F.2d at 1255, 195 USPQ at 433*. The 'Analysis Certificate, Reanalysis of the Lot no: E 003A' submitted by the Applicants does not establish that the phrase '>20 μg/dose of each of CFA/I, CS1, CS2, CS4 and CS5' excludes Applicants' claim limitation of 'at least 100 μg'.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

14) Claims 41-48 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 41 and 43 are redundant in the recitation: '*E. coli* ..... bacterial strain'. Since one of skill in the art would readily understand that *E. coli* strain is a 'bacterial' strain, it is suggested that Applicants delete the recitation 'bacterial'.

(b) Claim 40 is inconsistent with claims 41-48 in the limitation: 'oral vaccine composition'. Note that claims 41-48 recite the 'oral vaccine'.

(c) Claims 41-48 have improper antecedence in the limitation: 'The oral vaccine according to claim ....'. Claims 41-48 depend directly or indirectly from claim 40, which is drawn to an 'oral vaccine composition', as opposed to an 'oral vaccine'. It is suggested that Applicants delete the recitation 'composition' from the base claim 40, or replace the recitation in claims 41-48 with --The oral vaccine composition according to claim ...--.

(d) Claim 44 lacks proper antecedence in the limitation 'of CTB'. Claim 44 depends from claim 40, which already recites 'CTB'. Therefore, for proper antecedence, it is suggested that Applicants replace the limitation in claim 44 with --of the CTB--.

(e) Claim 45 lacks proper antecedence in the limitations: 'of CFA' and 'of CTB'. Claim 45 depends indirectly from claim 40, which already recites 'CFA' or 'CTB'. Therefore, for proper antecedence, it is suggested that Applicants replace the limitations in claim 45 with --of the CFA-- and --of the CTB-- respectively.

(f) Claim 48 is vague and/or lacks proper antecedence in the limitation: 'of r CTB'. Claim 48 depends from claim 47, which recites 'rCTB' as opposed to r CTB'. For clarity and proper antecedence, it is suggested that Applicants replace the limitation in claim 48 with --the rCTB--.

(g) Claims 41-48, which depend directly or indirectly form claim 40, are also rejected as being indefinite due to the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102 / 103

15) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

17) Claims 40-48 are rejected under 35 U.S.C § 102(a) as being anticipated by Savarino *et al.* (*J. Infect. Dis.* 177: 796-799, March 1998, already of record) as evidenced by Holmgren *et al.* (US 6,558,678, already of record), or in the alternative, as being unpatentable over Savarino *et al.* (*J. Infect. Dis.* 177: 796-799, March 1998, already of record) in view of Holmgren *et al.* (WO 92/14487, already of record) ('487), and Holmgren *et al.* (US 6,558,678, already of record) ('678) or Askelof *et al.* (WO 95/33825).

Savarino *et al.* disclosed an oral ETEC/rCTB vaccine produced by SBL Vaccin, Stockholm comprising formalin-inactivated ETEC SBL101 expressing CFA/I; SBL104 expressing CS4+CS6; SBL105 expressing CS5+CS6; SBL106 expressing CS1; and SBL 107 expressing CS2+CS3 mixed with 1.0 mg of rCTB, wherein ST is removed (see page 796; and Materials and Methods). Although Savarino *et al.* is silent about the exact amounts of the various CS or CFA antigens in the vaccine, the prior art vaccine is viewed as being encompassed within the scope of the instant claims, i.e., as anticipating the Applicants' vaccine for the following reasons. The five

enterotoxigenic ETEC strains comprised in the prior art vaccine are SBL101, SBL106, SBL107, SBL104 and SBL105, which are identical to the ETEC strains SBL101, SBL106, SBL107, SBL104 and SBL105 recited, for example, in claim 42. The amount or dose of the prior art vaccine was ~2 x 10^{10} formalin-inactivated bacteria of each of the above-cited ETEC isolates (see paragraph 2 under 'Materials and Methods'), which meets the vaccine dose used in the instant specification, i.e., approximately 10^{11} bacteria (see line 7 on page 3 of the instant specification). Therefore, the prior art vaccine dose is expected to contain 'at least 100 μg' of each of the antigens. Since the prior art ETEC SBL101 expressing CFA/I; SBL104 expressing CS4+CS6; SBL105 expressing CS5+CS6; SBL106 expressing CS1; and SBL 107 expressing CS2+CS3 present in a vaccine dose are the same as the ones recited in the instant claims, and are present in a dose of approximately 10^{11} bacteria, they are expected to contain at least 100 μg of the various CFA and CS antigens. The Office's position that the prior art vaccine anticipates Applicants' vaccine, or is encompassed within the scope of Applicants' vaccine is based upon the fact that every specific *E. coli* strain present in the prior art oral vaccine and Applicants' vaccine are the same. In spite of the fact that Savarino *et al.* are silent about the amounts of CFA or CS antigens in their vaccine, because the prior art vaccine dose of ~2 x 10^{10} formalin-inactivated bacteria of each of the ETEC meets the vaccine dose of 'approximately 10^{11} bacteria' used in the instant invention, there is sufficient overlap to reasonably conclude that the prior art vaccine anticipates Applicants' vaccine. Since the Office does not have the facilities for examining and comparing Applicants' ETEC strains with that of the prior art ETEC strains for exact quantities of CFA/CS antigens produced or contained therein, the burden is on the Applicants to show a novel or an unobvious difference between the instantly claimed vaccine and the prior art vaccine, i.e., to show that the prior art vaccine does not possess the same material and functional characteristics of the instantly recited vaccine. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzerald et al.*, 05 USPQ 594. Further, that the prior art oral ETEC/rCTB vaccine, produced by SBL Vaccin, is intrinsically contained in a buffered saline, is inherent from the teachings of Savarino *et al.* in light of what was known in the art at the time. For instance, Holmgren *et al.* ('487) disclosed that SBL ETEC/rCTB vaccine contained or was administered in a buffered

solution (see Example 5).

Claims 40-48 are anticipated by Savarino *et al.* The teachings of Savarino *et al.* anticipate the instant claims. Holmgren *et al.* ('678) is **not** used as a secondary reference in combination with Savarino *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Savarino *et al.* with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

Alternatively, if one viewed Savarino's disclosure as being non-anticipatory, then it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to increase the CFA or CS antigen production by the prior art ETEC strains using an art-known method of high-level expression of CFAs as the one taught by Holmgren *et al.* ('678) or Askelof *et al.*, to produce the instant invention with a reasonable expectation of success, since Holmgren *et al.* ('678) taught a method of growing high densities of the desired CFA- or CS-producing *E. coli* strains in a fermentor or liquid medium, without loss in the ability to express different CFAs including CFA/I, CFA/II and CFA/IV, such that the strains show high-level expression of the CFAs, followed by the safe inactivation of the resultant *E. coli* without destroying the CFAs (see columns 5-8; and Examples of the '678 patent) and quantifying the CFA antigens on *E. coli* strains using a quantitative CFA inhibition ELISA (see paragraph bridging columns 6 and 7), or since Askelof *et al.* taught how to cultivate ETEC strains such that they express CFA and CS antigens before the loss of plasmids that code for the antigens (see 'Description of the Invention' and claims). One of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing optimal or increased quantities of the CFAs on the *E. coli* present in Savarino's vaccine composition, since *E. coli* strains expressing optimal quantities of the antigens are ideally desired in a vaccine.

With regard to the recitation 'at least 100 μg of at least three different types' of CFAs, the process of optimizing, or increasing the amount of CFAs on *E. coli* to a desired amount in an art-known vaccine was well within the realm of routine experimentation and would have been obvious to a skilled artisan at the time of the instant invention. It has been held legally obvious and within the routine skill in the art to optimize a result-effected variable. In the instant case, the

amount or concentration of at least three types of CFAs in the vaccine is clearly a result-effected variable, and it would have been obvious to vary or optimize the CFA antigenic content as desired, in the prior art vaccine, for example to 100 μg or greater, by routine experimentation, since methods of increasing the CFA expression on *E. coli* were known in the art at the time of the invention, as taught by Holmgren *et al.* ('678) or Askelof *et al.*

Remarks

18) Claims 40-48 stand rejected.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (703) 872-9306.

20) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

S. DEVI, PH.D.
PRIMARY EXAMINER